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Outcome after renal transplantation. Part I: intellectual and motor performance

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Outcome after renal transplantation.

Part I: Intellectual and motor performance

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Abstract Comprehensive information on neurodevelopmental outcome in children and adolescents with chronic kidney disease is still limited. Intellectual performance (IP) and motor performance (MP) were systematically assessed in 27 patients at a median age of 14.1 years (range 6.5–17) and 6 years (range 0.5–12.7) after renal transplantation (RTPL). IP was analyzed with the Wechsler Intelligence Scale for Children-III (WISC-III) in 25 patients and by the Kaufman Assessment Battery for Children in two patients. MP was evaluated by the Zurich Neuromotor Assessment. Median full-scale intelligent quotient (FSIQ) was 97 (range 49–133). Twenty-one patients had an FSIQ \geq 85 (i.e. \geq mean–1 standard deviation). The five patients with neurological comorbidity had a median FSIQ of 81 (range 49–101). Verbal IQ (VIQ) (median 104; range 50–146) was significantly ($p < 0.01$) higher than performance IQ (PIQ) (median 88; range 48–117). The PIQ was significantly lower compared with controls ($p < 0.007$), and patients scored significantly lower compared with controls in five of 11 subtests of the Wechsler Scale. All MP tasks were significantly ($p < 0.01$) lower than in controls, and also in

children without neurological comorbidity. Socioeconomic status was significantly correlated with FSIQ ($p = 0.03$). IP after RTPL was within the normal range for the majority of children. PIQ was lower compared with VIQ, and MP was significantly affected in all children after RTPL.

Keywords Renal transplantation · Outcome · Intellectual performance · Motor performance · Neurodevelopmental outcome

Introduction

Comprehensive data on neurodevelopmental outcome, i.e. intellectual performance (IP) and motor performance (MP), in children with chronic kidney disease [1–6] and in particular after renal transplantation (RTPL) [2, 7–10] are still limited. Published studies have focussed either on IP [1–5, 7] or on MP [6, 8], and only a few studies have assessed both [9, 10].

The majority of the children on dialysis had IP scores in the lower normal range [1, 2]. Increased disease severity, longer disease duration, and younger age at onset of kidney disease potentially placed children with chronic kidney disease at increased risk of neurocognitive deficits [5]. Further associations of impaired IP were younger age at the start of renal replacement therapy and longer duration of dialysis [1, 5]. Children showed improvement in specific aspects of IP after RTPL (e.g. mental processing speed and sustained attention) compared with those on dialysis [4, 7, 10]. In infants transplanted before the age of 30 months, comparison of individual cognitive and motor function revealed an improvement in both areas after RTPL [10]. However, mainly global measures of intelligence were used, and subdimensions of intelligence such as verbal

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intelligence quotient (VIQ) and performance IQ (PIQ) were not systematically analyzed [5, 9].

Assessment of neuromotor function only included technical examinations, such as electroencephalograms, computed tomographic scan, magnetic resonance imaging, and nerve conduction velocity, indicating neurological deficits in up to 20% of transplanted children [9]. To date, no study has assessed MP in school-aged children using a standardized motor assessment battery. A preliminary study from our unit had shown that MP was significantly impaired in children starting renal replacement therapy before 5 years of age [11].

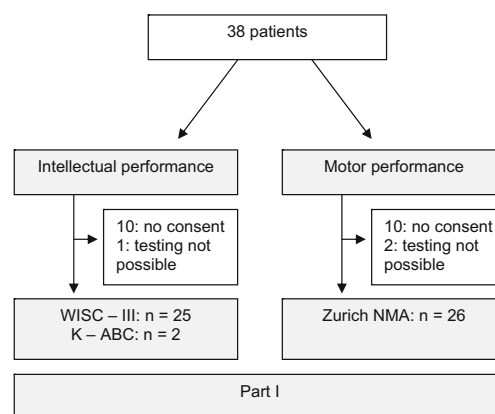
Some studies were based on a small number of patients [1, 7] or focused only on special risk groups by including children suffering from chronic kidney disease at a young age (3 months to 5 years) [1, 3, 9, 10]. Other authors [3, 9] demonstrated that children may manifest a variety of major or minor neurological complications ranging from cerebrovascular events to reduced head circumference size. It is thus conceivable that motor impairment may be found in children after RTPL also in the absence of major neurological events, reflecting milder neurological injury. Additionally, we and others [12] have shown that IP and MP may be related in children at risk for neurodevelopmental impairments, such as prematurely born children. We thus aimed to determine this relationship in children after RTPL.

The aim of this study was to assess IP and MP in children and adolescents after RTPL using standardized and validated methods. Additionally, medical, socioeconomic, and family-related predictors (e.g. marital status, mother tongue, number of siblings) of IP and MP were evaluated.

Methods

Patients

Forty patients underwent RTPL at our hospital between 1995 and 2005. Inclusion criteria were RTPL, age > 5 years at examination, and follow-up at our unit. Neurodevelopmental outcome was evaluated in 27 (15 boys, 12 girls) out of 38 eligible patients (Fig. 1). The underlying diseases were acquired, congenital, or inherited in six, eight, and 13 patients, respectively. Five patients had neurological comorbidity: neonatal hypoxia (1), cerebral infarct (1), severe deafness (1), severe visual impairment (1), and Joubert syndrome (1). Three patients were born prematurely. Thirteen patients did not participate: two had died with good graft function and one had severe neurological deficit (neonatal cerebral infarct) and could not be adequately examined, and parents did not provide consent for ten patients. Two of these children were born prematurely; none had a neurological comorbidity.



WISC – III: Wechsler Intelligence Scale for Children-III

K – ABC: Kaufman Assessment Battery for Children

Zurich NMA: Zurich Neuromotor Assessment

Fig. 1 Algorithm of all 38 surviving patients transplanted between 1995 and 2005. Included in Part I: 27. Age at transplantation: 2–15 years; age at evaluation: 6–17 years

Immunosuppression at examination consisted of cyclosporine A (17; trough level 80–120 ng/ml) or tacrolimus (10; trough level 4–8 ng/ml), mycophenolate mofetile (19; dose 1,200 and 900 mg/m² body surface in patients on cyclosporine A and tacrolimus, respectively) or azathioprine (7; dose 1 mg/kg body weight), and low-dose alternate-day prednisone (range 2.5–5.0 mg per dose; 21). Six patients were off steroids.

Renal function was assessed as estimated glomerular filtration rate (GFR: ml/min per 1.73 m² body surface area) calculated by the Schwartz formula with a *k*-factor of 40 based on local comparison with Cr-EDTA clearance measurements [13]. Casual blood pressure was measured in the sitting position. Indication for antihypertensive treatment was a systolic blood pressure >95th percentile [14]. At the time of evaluation, systolic blood pressure of all patients was <95th percentile. Height, weight, and body mass index (BMI: kg/m²) were correlated to normative Swiss data [15].

Assessment of intellectual performance (IP) and motor performance (MP)

The examination of IP and MP took a full morning (09.00–13.00). The order of examination was: Joining phase, IP testing, break, MP testing, and neurological examination.

Wechsler Intelligence Scale for Children-III (WISC-III)

The Wechsler Intelligence Scale for Children-III (WISC-III) is used in children aged 6–16 years (school age) and is organized into three IQ scores: full-scale IQ (FSIQ), VIQ, and PIQ, with a mean score of 100 and a standard deviation

(SD) of 15. In this study, children were examined with the WISC-III [16, 17]. The WISC-III consists of VIQ and PIQ, which form the FSIQ. The VIQ is composed of subtest information, comprehension, arithmetic, similarities, and vocabulary; the PIQ consists of the subtests coding, picture completion, picture arrangement, block design, and object assembly. The subtest digit span is a separate subtest, which is not included in the verbal subtest. The VIQ and PIQ are combined into the FSIQ. In Switzerland, normal age at entry in primary school is 6–7 years, and an FSIQ > 85, i.e. \geq mean–1 SD, is mandatory to attend normal school.

Kaufman Assessment Battery for Children (Kaufman-ABC)

The Kaufman Assessment Battery for Children (K-ABC) is used in preschool children and is composed of two parts: the mental processing composite and the achievement scale [18, 19].

Zurich Neuromotor Assessment (Zurich NMA)

The Zurich Neuromotor Assessment (NMA) is a standardized and reproducible testing procedure assessing timed performance and associated movement quality of a variety of motor tasks. Age- and gender-specific normative data are based on 662 healthy children and adolescents recruited from the local Zurich and aged between 5 and 18 years [20, 21]. The testing procedure includes assessment of pure motor tasks, adaptive fine-motor tasks, adaptive gross-motor tasks, static balance, and stress gaits [20, 21]: *Repetitive, alternating, and sequential movements* were assessed by the performance of finger, hand, and foot movements, alternating hand pronation–supination and foot movements, and sequential finger movements. *Pegboard* examination was conducted according to age. *Dynamic balance* was analyzed by an elastic cord fixed 20 cm above the floor between two metal poles placed 4 m apart. The exercise consisted of two tasks: the first was side-to-side jumping keeping the feet together; the second was forward jumping. *Static balance* was assessed by asking the child to choose one leg and stand on it for as long as possible, time limit 60 s. For this analysis, only time performance was used. The child's performance is videotaped and timed with a watch. The results of the Zurich NMA are expressed as four motor components: (1) the pure motor component combines the timed performance of all repetitive, alternating, and sequential movements of both extremities; (2) the adaptive fine-motor component combines all timed performances of the peg board; (3) the adaptive gross-motor component combines the results of the dynamic balances; and (4) the static balance. Intraobserver reliability for timed performance of the components pure motor, adaptive fine motor, gross motor, and static balance is 0.95, 0.99, 0.99,

and 0.99, respectively [20, 21]. The intraobserver reliability is derived from the normative sample. All Zurich NMA tasks are expressed as standard deviation score (SDS or Z score) derived from the age- and gender-related reference population.

Socioeconomic status (SES)

Socioeconomic status (SES) can be defined by a variety of factors. We used paternal employment and maternal education for defining SES. SES was defined and validated for Swiss children and is expressed by the sum of a six-point scale of paternal occupation and maternal education [22]. The method has already been used in other studies assessing the influence of SES on intellectual outcome [12].

Procedure

The study was approved by the Ethical Committee of the University Hospital of Zurich, and written informed consent was obtained from all parents and patients older than 10 years. All 27 patients were tested by one pediatrician, who was not involved in the patient care and was unaware of the current graft function. The examiner was supervised by video recordings.

Statistical analysis

The analyses were performed using the SPSS statistical software package (Version 11.5, SPSS Inc, Chicago, IL, USA). Data are presented as mean (\pm SD) or median (range) if data were not normally distributed. The null hypothesis tested against was that children with RTPL had no impairment of IP and MP in comparison with healthy children. Differences between groups were analyzed using Student's *t* test or Mann–Whitney *U* test, depending on data distribution. To evaluate associations of IP and MP, Spearman's rank correlation coefficients were computed. Univariate analysis was followed by multiple regression analysis to determine the independent association between PIQ and MP. Proportions between the groups were compared by Fisher's exact test. A *p* value of < 0.05 was considered significant.

Results

Clinical evaluation

Twenty-seven patients were examined at an age of 14.1 years (range 6.5–17) and 6 years (range 0.5–12.7) after RTPL (Tables 1 and 2). Estimated glomerular filtration

Table 1 Clinical data of 27 patients

Parameter	Median (range) or number of patients
Gender (male/female)	15/12
Age (years) at investigation	14.1 (6.5–17)
Age (years) at RTPL	9.2 (2–15)
Living related RTPL/deceased donor	17/10
Follow-up time since RTPL (years)	6 (0.5–12.7)
Glomerular filtration rate (ml/min per 1.73 m ²)	81 (32–115)
Height SDS	−0.9 (−2.9 to 0.8)
BMI SDS	0.16 (−1.4 to 1.9)
Age (years) at onset of dialysis (<i>n</i> =19)	7.7 (0.25–15)
Haemodialysis/peritoneal dialysis before RTPL	8/11
Duration (years) of dialysis (<i>n</i> =19)	1.4 (0.2–4.6)
With/without neurological comorbidity	5/22

RTPL renal transplantation, SDS standard deviation score, BMI body mass index

rate was 81 ml/min per 1.73 m² (range 32–115), and 14 patients were on antihypertensive medication.

School performance

Median age at school entry was 7.3 years (6.3–7.8) and was comparable in patients with and without neurological comorbidity. Two children attended the nursery at the time of evaluation. Nine of 25 children had repeated a school grade, and three attended a special first class taking 2 years instead of 1 year. Four of five children with neurological comorbidity went to a special school, whereas all school-aged children without neurological comorbidity (*n*=20) attended normal school (Fisher's exact test, *p*=0.0007).

Intellectual performance (IP)

WISC-III was examined in 25 patients (Tables 2 and 3): Median FSIQ in all tested children was 97 (49–133), with

Table 2 Diagnosis, intellectual performance, and risk factors of all 27 patients

Patient	Diagnosis	Full scale IQ	Verbal IQ	Performance IQ	Risk factors
1	Renal dysplasia	81	86	80	–
2	Renal dysplasia and PUV	95	108	84	–
3	Renal dysplasia	109	110	104	–
4	Denys-Drash-syndrome	112	110	112	–
5	Neonatal shock kidneys	76	78	75	Neonatal asphyxia
6	ARPKD	102	118	85	–
7	Atypical HUS	85	88	85	–
8	Bone marrow transplantation associated renal failure	81	89	76	Cerebral infarct
9	Renal dysplasia and PUV	132	140	117	Premature birth (36 week)
10	Renal-hepatic-pancreatic dysplasia	88	K-ABC	K-ABC	–
11	FSGS	101	118	84	Premature birth (36 week)
12	DMS	101	K-ABC	K-ABC	Severe visual impairment
13	FSGS	103	117	88	–
14	Cystinosis	100	104	97	–
15	IgA-nephropathy	106	117	92	Premature birth (34 week)
16	Joubert syndrome	49	50	48	Joubert syndrome
17	Cystinosis	71	76	68	–
18	Branchio-oto-renal syndrome	85	85	89	Severe deafness
19	Renal dysplasia and PUV	90	95	88	–
20	Denys-Drash-syndrome	133	146	109	–
21	Renal dysplasia	97	109	85	–
22	Cystinosis	99	104	95	–
23	FSGS	87	89	88	–
24	Nephronophthisis	109	113	101	–
25	Renal dysplasia and PUV	88	97	81	–
26	FSGS	114	117	107	–
27	1° Hyperoxaluria	75	82	69	–

IgA Immunoglobulin A, PUV posterior urethral valves, ARPKD autosomal recessive polycystic kidney disease, HUS hemolytic uremic syndrome, FSGS focal segmental glomerulosclerosis, DMS diffuse mesangial sclerosis, K-ABC Kaufman Assessment Battery for Children

Table 3 Intellectual performance (only Wechsler Intelligence Scale for Children-III): data given for all 25 children and 20 children without neurological comorbidity

	IQ subscales (n=25)	P value*	IQ subscales (n=20)	P value*
Full-scale IQ	97 (49–133)	0.173	100 (71–133)	0.760
Verbal-scale IQ	104 (50–146)	0.663	109 (76–146)	0.089
Information	10 (1–19)	0.283	10 (4–19)	0.953
Comprehension	10 (3–19)	0.492	11 (5–19)	0.153
Arithmetic	9 (1–15)	0.521	10 (5–15)	0.484
Similarities	12 (2–18)	0.028	13 (3–18)	0.015
Vocabulary	11 (1–19)	0.796	12 (4–19)	0.121
Digit span	8 (1–13)	0.001	8 (1–13)	0.003
Performance-scale IQ	88 (48–117)	0.001	88 (68–117)	0.007
Coding	8 (1–15)	0.015	8 (4–15)	0.049
Picture Completion	8 (2–13)	0.001	8 (2–13)	0.001
Picture arrangement	9 (1–17)	0.207	10 (1–17)	0.807
Block design	9 (1–17)	0.178	9 (1–17)	0.576
Object assembly	6 (1–12)	0.001	6 (2–12)	0.001

IQ intelligence quotient

* Univariate *t* test compared with normative data [17]

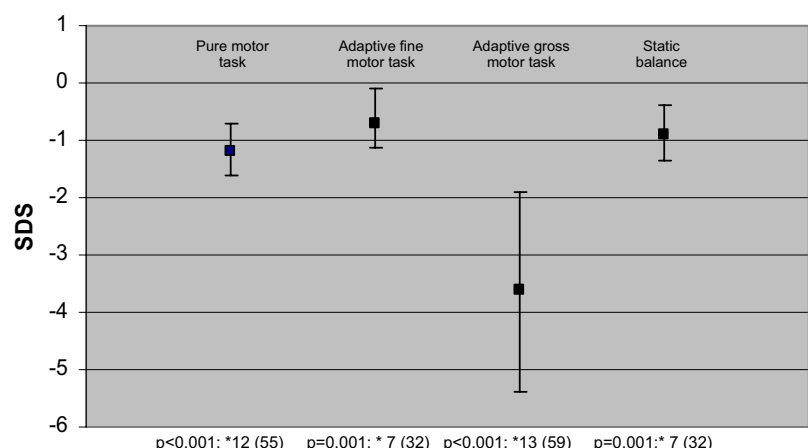
VIQ and PIQ of 104 (50–146) and 88 (48–117), respectively. Nineteen, two, and six children had an FSIQ between 85 and 115 (i.e. mean \pm 1 SD), > 115 and < 85 , respectively. The five patients with neurological comorbidity had a median FSIQ of 81 (range 49–101).

VIQ was significantly ($p < 0.01$) higher than PIQ. The PIQ was significantly ($p < 0.007$) lower compared with controls. The patients also scored significantly lower compared with controls in five of the 11 subtests, i.e. similarities, digit span, coding, picture completion, and object assembly ($p < 0.05$). The scoring was also significantly lower ($p < 0.05$) when patients with neurological comorbidity were excluded. Two preschool children without neurological comorbidity were assessed with the K-ABC, resulting in an FSIQ of 88 and 101, respectively.

Motor performance (MP)

MP could be assessed in 26 of 28 eligible patients. Two patients with severe neurological comorbidity (Joubert syndrome and severe cerebral infarct) could not be formally tested. Significant impairment compared with healthy children was observed in all four motor components (Fig. 2). The proportion of children with impaired MP, defined as values < 10 th percentile, ranged from 32% to 60%. The five patients with neurological comorbidity had significantly lower scores in all tasks compared with 21 patients without comorbidity ($p < 0.01$). MP was also poorer in children without neurological comorbidity compared with controls (one-sample *t* test: pure motor task $p < 0.001$, adaptive fine motor $p = 0.01$, adaptive gross motor $p < 0.001$, static balance $p = 0.001$).

Fig. 2 Motor performance [Zurich Neuromotor Assessment (Zurich NMA)] of 26 patients after renal transplantation: data given as standard deviation score (SDS): mean and 95% confidence interval



*Number of patients (%) below 10th percentile.

Socioeconomic status (SES)

Mean SES in this sample was 7.3 (range 3–12).

Associations of intellectual performance (IP) and motor performance (MP)

Patients without neurological comorbidity or further risk factors for development (e.g. premature birth, cerebral infarct, neonatal asphyxia, visual impairment, and deafness) had higher scores for IP and MP compared with patients with comorbidity or risk factors. Neurological comorbidity was negatively associated with FSIQ (Mann-Whitney *U* test $p=0.03$). There was a significant association between PIQ and pure-motor (Spearman: $r=0.45$; $p=0.03$) and adaptive fine-motor (Spearman: $r=0.50$; $p=0.01$) tasks. After adjusting for neurological comorbidity, the association between PIQ and MP (both pure and adaptive fine motor) was no longer statistically significant. SES was significantly associated with FSIQ (Spearman: $r=0.41$; $p=0.03$), but not with MP. Patient-, family-, and illness-related variables, e.g. glomerular filtration rate, prednisone therapy, age at onset and duration of dialysis, and age at RTPL, were not significantly associated with IP and MP. There was also no gender-related difference in MP or IP.

Discussion

Long-term outcome after RTPL in children, i.e. patient and graft survival, has steadily improved over the last decades [23, 24]. However, information on comprehensive and detailed neurodevelopmental outcome after RTPL is still limited [1–9]. This cross-sectional study presents detailed measures of IP and MP in children after RTPL.

The majority of our patients scored an FSIQ within the lower normal range. This observation is consistent with other studies [1, 2, 4, 5, 7, 9]. Studies analyzing only IP differed significantly in their design [1–5, 7]. Focusing on 15 infants initiating long-term peritoneal dialysis in the first year of life, median FSIQ was in the lower normal range (91, range 50–102), and only one patient had an FSIQ above mean (> 100) [1]. Similar results were obtained by Warady et al. who evaluated 28 children undergoing peritoneal dialysis at the very young age of ≤ 3 months. General mental development scores were in the average range (defined as 85–115) in 79% of the children tested > 4 years of age [3].

PIQ was significantly lower than VIQ in our patients. These findings are in line with previous studies [6, 8]. Although not statistically significant, PIQ after RTPL was associated with MP as assessed by the Zurich NMA. However, the primary reasons for impaired MP in

children suffering from chronic kidney disease remain unclear.

In our series, IP was not correlated with illness-related variables, e.g. age at onset of dialysis, duration of dialysis, age at RTPL, graft function, and prednisone therapy. These results are at variance with reports showing that disease severity, longer disease duration, and younger age at onset of kidney disease were significant clinical predictors of IP [2, 5]. In particular, children with increased disease severity and a low glomerular function were potentially placed at increased risk of neurocognitive deficits [5]. Explanations for the absent impact of illness-related variables include the rather homogeneous population, with the majority of children having a good graft function and the fact that neurodevelopmental evaluation was performed 6 years after RTPL. A long interval since RTPL may efface a correlation between pretransplantation factors and IP and MP. However, the fact, that this analysis only included patients after RTPL implies caution by extrapolating conclusions and represents an acknowledged limitation of our data. Consistent with other reports, SES was significantly correlated with IP [22].

This study reports the first comprehensive analysis of MP after RTPL using a standardized and validated method (Zurich NMA). Motor performance was significantly impaired in the transplanted children and adolescents—also in patients without neurological comorbidity—with 32–59% of patients scoring < 10 th percentile in all components. Specifically, the pure motor task and the adaptive gross-motor component were mostly affected. Impairment of the pure-motor task and the adaptive gross-motor task may lead to clumsiness in school-aged children and therefore substantially negatively affect their academic performance and competence in other developmental areas, such as communication and social interaction with peers, and thus profoundly influence feelings of well-being and self-esteem.

General muscular hypotonia has also been observed in nine, four, and two children with chronic kidney disease, on dialysis, and after RTPL, respectively [6]. Motor performance assessed by the Bayley Scales of Infant Development was normal in 76% of children transplanted at an age < 5 years, and similar to our own findings, neurological comorbidity was the most negative predictor [9].

Patient- and illness-related variables, e.g. glomerular filtration rate, prednisone therapy, age at onset and duration of dialysis, and age at RTPL, had no significant association concerning IP and MP in our patients, whereas SES was the only predictor of IP. Neurological comorbidity was the most significant correlating factor negatively influencing both IP and MP. There are a variety of reasons for neurological comorbidities in patients with chronic renal diseases, e.g. cerebral infarct, neonatal asphyxia, syndromic maldevelopment of the brain, visual impairment, and deafness.

Few studies have assessed patients longitudinally before and after RTPL [4, 7, 10]. One study reported an improvement of cognitive and psychomotor function after RTPL [10], whereas there was no difference in FSIQ. A further study showed that transplanted patients did significantly better in achievement tests of written language and in school performance [4]. Mental processing speed and sustained attention improved in nine children after RTPL [7]. Taken together, the majority of these longitudinal observations suggest that successful RTPL has a significant impact on neurodevelopment performance.

Our cross-sectional study of neurodevelopmental outcome in children after RTPL confirmed our hypothesis. It indicates a normal intellectual functioning for the majority of patients in the majority of subtests but a significantly impaired MP. Neurological comorbidity is associated with MP and IP. The lower PIQ might be related to impaired MP. A detailed neurodevelopmental and motor assessment of children with chronic kidney disease provides both the possibility of defining their specific requirements and of developing promotional programs individually focussed on these children.

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